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Director of RWS Group Ltd, of Europa House, Marsham Way, Gerrards Cross, Buckinghamshire, England declare;

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2. That the translator responsible for the attached translation is well acquainted with the French and English languages.

3. That the attached is, to the best of RWS Group Ltd knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in France on 21 January 1997 under the number 97/00,803 and the official certificate attached hereto.

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For and on behalf of RWS Group Ltd

The 15th day of October 2004

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54 COSMETIC OR DERMOPHARMACEUTICAL PRODUCTS WHICH ARE COMPATIBLE WITH THE CUTANEOUS ECOLOGY

57

Cutaneous interactive base, characterized in that it essentially comprises biodermal constituents which are cytocompatible with the skin, the said interactive base expressing at least one topical biological activity which is identical to or different from the biological activity of at least one biodermal constituent, and having a composition which gives it a stable topical pharmaceutical form.

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The present invention relates to cosmetology, body-hygiene, topical dermotherapeutics and, in general, any product intended for the skin.

In general a cosmetic or dermatological product comprises one or more active principles and an excipient or vehicle in which the active principle(s) is (are) distributed or dispersed, the whole being formulated for topical application, for example in the form of a gel or cream.

The term "active principle" means any compound, any composition or any product which exerts biomechanical, biophysical, physiological or biological activity on the skin, and in particular on the epidermis, and which has any physicochemical form or nature required for the treatment or action chosen or selected with respect to the skin.

At the present time, to the Applicant's best knowledge, nobody has been concerned, for cosmetic or therapeutic purposes, in the skin, and in particular the epidermis, considered as an ecological medium or system, with the exception of certain studies relating only to the ecology of the cutaneous bacterial flora.

This is the subject of the present invention.

In its general aspect, the invention proposes a new generation of cosmetic or corporal hygiene or dermotherapeutic products which comprise at least 98% by weight of a cutaneous interactive base. This base comprises essentially or consists of several biodermal constituents, each chosen for their biocompatibility and cytocompatibility with skin cells, and preferably biomimetic with a component of the skin, in particular of the epidermis. These biodermal constituents are chosen and formulated, on the one hand, in order together to express at least one topical biological activity, which is identical to or different from the biological activity of at least each biodermal constituent, and, on the other hand, in order to end up with a topical form which is stable as regards the practical or technical function in question, for

example gel, milk, cream, lotion or make-up remover, for a body hygiene or cosmetic product.

It results from the above definition, by difference with the conventional cosmetic or dermatological products, that it is no longer possible in particular to distinguish between active principle(s) and excipient or vehicle. In practice, the cutaneous interactive base behaves both as one or more active principles and as an excipient. Furthermore, each biodermal constituent must be considered equally as a constituent of the skin and/or an active principle and/or a pharmaceutical agent, for example a thickener or a surfactant.

Preferably, the cutaneous interactive base represents the entire weight composition of the product considered.

Preferably, the cutaneous interactive base is composed primarily by weight, for example to at least 90%, more preferably 98% by weight, of one or more biodermal constituents which are biomimetic with a component of the skin and whose amount by weight in the said base (expressed as a weight percentage for example) is different from that of the said component in the skin. When the cutaneous interactive base is not composed entirely of the biomimetic constituent or constituents, its composition is completed by a biodermal regulatory constituent.

By way of example, the cutaneous interactive base comprises at least two biodermal and biomimetic constituents, the major one of which is a constitutive component of the epidermis and the minor of which is a skin nutrient.

Advantageously, the biodermal constituent is chosen from the biological, mineral, organic or biochemical species or entities of which the epidermis is composed. By way of example, one of the biodermal constituents is chosen from skin nutrients.

In accordance with the invention, for example, the cutaneous interactive base is a two-phase or

single-phase base and is composed of a water-in-oil emulsion or oil-in-water emulsion or a continuous oily phase or continuous aqueous phase, in order to form any appropriate topical form, for example cream, emulsion, lotion, etc.

The term "cutaneous interactive base" refers to any composition having the property by which it maintains all the functional biological equilibria of the skin, without inhibiting or exacerbating them, this being in addition to the topical biological activity of the said composition, resulting from the synergistic or non-synergistic biological activity on the skin of one or more biodermal constituents.

A cutaneous interactive base according to the invention thus has both a primary function and a secondary function. The primary function consists in both protecting and maintaining, or even in restoring, the main biological and physiological cutaneous equilibria, and in creating a suitable stable pharmaceutical form (milk, cream, etc.). The secondary function consists in treating the skin by providing it with one or more topical benefits, in particular therapeutic or cosmetic benefits.

The term "pharmaceutical form" means any form or presentation which allows the cutaneous interactive base to exert functional activity on the skin.

The term "biodermal constituent" means any component or product forming part of the composition of the skin, in particular of the epidermis, it being understood that this constituent is considered in isolated form, irrespective of the method by which it is obtained or produced, in particular by separation from live skin products, by chemical synthesis, or by genetic recombination.

The term "biologically active" refers to the fact that the component or constituent considered itself displays biological activity in the epidermis, or alternatively participates in any biological process, such as metabolism, in the epidermis.

The term "topical activity" refers to the fact that, globally, the cutaneous interactive base exhibits or manifests, via the topical route, a cosmetic or therapeutic benefit on the skin, for example on the epidermis.

The expression "cytocompatible with the skin" refers to the property by which the biodermal constituent selected has a cytotoxicity of less than 10% with respect to a cell culture of human keratinocytes, i.e. it remains virtually neutral with respect to the cellular viability and morpho-differentiation of the keratinocytes.

This cytocompatibility can be evaluated by means of the following routine test.

Normal human keratinocytes obtained from plastic surgery are cultured in sub-emerged condition in defined medium (MCDB 153) supplemented with 10 ng/ml of an epidermal growth factor, 5 µg/ml of insulin, 0.1 mM ethanolamine, 0.1 mM phosphoethanolamine and 2% of non-essential amino acids. This medium allows keratinocytes to be cultured without the presence either of serum or of live nourishing cells (3T3 fibroblasts); its low calcium content (0.1 mM) promotes cell growth.

The biodermal constituents are evaluated as regards their capacity to induce cytopathic effects on sub-confluent cultures. The contact times are 6 hours, 12 hours, 24 hours and 36 hours.

The cell viability is measured quantitatively by indirect counting of the live cells after labeling them with a vital dye. The neutral red system (3-amino-7-dimethylamino-2-methylphenasine hydrochloride) measures the activity of passage of the dye across the plasma membrane and of storage in the lysosomes of the viable cells.

The total incorporation of the neutral red is proportional to the number of live cells in culture.

The dye incorporated is extracted with an acetic acid/ethanol solvent and quantified by

spectrophotometric measurement. The results are compared qualitatively, relative to culture standards, and are expressed as optical density (OD) and/or percentage of optical density relative to the negative control (untreated culture).

Within the variation limits of the strains used, a percentage of greater than or equal to 90% optical density for a culture placed in contact with the test biodermal constituent, relative to the negative control, indicates that the said constituent is cytocompatible with the skin.

The term "biomimetic" refers to the fact that the biodermal constituent selected has the structure and/or exerts the biomechanical, biophysical, physiological or biological function or activity of any skin component, i.e. of any skin component which can be isolated or separated by fractionating the dermis and/or the epidermis, or alternatively of any component whose existence can be characterized or demonstrated in the dermis and/or the epidermis, or alternatively of any component which can be assimilated by the skin and serve, if need be, as a nutrient for the constituent cells of the skin.

In other words, the skin, as a live biological medium, cannot distinguish between its own biodermal constituents and the biomimetic constituents, apart from any atypical, allergic or immunogenic reaction.

Preferably, the biodermal constituents are chosen from biological, inorganic, organic or biochemical species or entities which constitute the skin, irrespective of the effective origin of the constituents brought onto or into the skin.

The biodermal constituents can be chosen from the constituent molecules of the epidermis and of the dermis. By way of example, the following will be selected:

- various fluid or solid lipids, such as oleic acid, essential fatty acids, mono-, di- and

triglycerides, linoleic acid, squalene, stearic acid or glyceryl monostearate,

- solid lipids, such as stearic acid, cholesterol, ceramides, cholesterol ester or sulphate, or saturated diglycerides,
- nucleic acids,
- mucopolysaccharides such as hyaluronic acid,
- collagens.

The biodermal constituent can also be chosen from skin nutrients, i.e. compounds or compositions which can be metabolized by skin cells.

By way of example, mention will be made of all the elements, or fragments of foods, which are useful for the metabolism of the skin, such as cutaneous acids, fatty acids and vitamins.

By "regulatory biomimetic constituent" is meant a constituent which contributes to maintaining constant at least one physical, chemical, biochemical or biological condition of the skin.

If necessary, the composition of a cosmetic, corporal hygiene or dermopharmaceutical product according to the present invention can be supplemented, to a maximum amount of 2%, with non-biodermal constituents which are foreign to the skin, and which are necessary for the pharmaceutical formulation of the said product. By way of example, mention will be made of fragrances and certain minor adjuvants required for the correct maintenance of the stability and purity of the cutaneous interactive base.

The cutaneous interactive base forming virtually all, if not all, of the product according to the invention is formulated and obtained according to traditional techniques, and is for example a two-phase base, consisting of a water-in-oil or oil-in-water emulsion.

Tables 1 to 3 collate examples of biodermal constituents for formulating an oily phase, and/or an aqueous phase, and supplementing the formulations depending on the applications of the cosmetic product.

In these tables, the left-hand column indicates a recommendation, it being understood that, as stated previously, each of the biodermal constituents is by nature cytocompatible with the skin, and biomimetic with the latter. The other columns indicate the class to which the said component belongs, according to the following classification:

Class 1:

Substantially cytocompatible and/or bio-assimilable components, present in constitutional form in the skin (water, amino acids, trace elements, vitamins, etc.).

Class 2:

Macromolecules obtained by biotechnological means, synthesis or extraction process, which are identical or virtually identical to the constituents of the skin (sodium salt of DNA, sodium hyaluronate, etc.) in composition and structure. These compounds are cytocompatible with the skin, but they can exhibit metabolic interactions in the context of biological or physiological processes. However, their biological action is comparable to that of the components naturally present in the skin (biomimetism).

The components of classes 1 and 2 are interactive, i.e. they act both as active agents and as excipients.

Class 3:

Components which are useful to and assimilable by the skin, if possible of food or dietary origin, or alternatively authorized in foodstuffs, but they must be cytocompatible. These components are interactive: they act both as "dermo-dietary" agents and as excipients.

Class 4:

Inert components, i.e. components which do not bring about any chemical, biological or immunological effect on the skin: compounds remaining in the superficial cellular strata of the epidermis (for

example petroleum jelly and other fatty substances of mineral origin, silicones, etc.).

Class 5:

Components which irrespective of their origin (plant, synthetic, extraction, biotechnology) are completely cytocompatible (total absence of signs of cytotoxicity) and which do not give rise to any allergic reaction.

TABLE 1

NATURE OF THE COMPONENTS	(1)	(2)	(3)	(4)	(5)
Fluid lipids	oleic acid (XX) linoleic acid (XX) squalene (XX)	triglycerides (XXX)	plant oils (XX or XXX depending on the oil used)	liquid petroleum jelly (XXX)	
Solid lipids	stearic acid (XX) palmitic acid (XX) cholesterol (XX) cholesterol ester (XX) cholesterol sulfate (XX) ceramides (X)		palm oil (XX) beeswax (XX)	white petroleum jelly (XXX)	lanoline (XXXX)
Radical-scavenging antioxidants	tocopherols (XX) citric acid (XX) glutathione (XX) superoxide dismutase (X)		bioflavonoids (X)		

CUTANEOUS CYTOCOMPATIBILITY SCALE

X	0-1%
XX	1-10%
XXX	10-50%
XXXX	>50%

TABLE 2

NATURE OF THE COMPONENTS	(1)	(2)	(3)	(4)	(5)
Surfactants	glycolipids (XX) lecithins (XX) glycosylceramides (XX) lysine stearate (XX) arginine stearate (XX) lysine oleate (XX)	sophorolipids (XX)	lipoproteins (XX)		sorbitan palmitate (X) sorbitan oleate (X)
Thickeners Gelling agents	hyaluronic acid (X) DNA (XX)	mucopolysaccharides (XXX)	xanthan (XXXX) pectin (XX) starch (XX)	chitin (XX)	hyroxypropyl-celulose (XX)
Wetting agents	glycerol (XX) urea (XX) serine (XX) glucose (XX)		fructose (XX)		propylene gycol (XX)
Antiseptics	short-chain fatty acids (X) lactoferrin/ lactoperoxidase (X)		propolis (X)		phytic acid (X) sorbic acid (X)

TABLE 3

NATURE OF THE COMPONENTS	(1)	(2)	(3)	(4)	(5)
Dyes	vitamin B (X) flavins (X)		carotenoids (X) caramel (X)		anthocyans (X)
Sunscreens and sunblocks	DNA (XX) pyrimidine bases (XX) melanins (XX)			titanium oxide (X) zinc oxide (XX)	chlorogenic acids (X) polyphenols (X) ferulic acid (X)
Fragrances			essential oil of lavandin (X)	flower water (XX)	
Minerals	sodium (XX) calcium (XX) magnesium (XX)				
Trace elements	iron, copper (X) zinc (XX) selenium (X)				

The compositions of a number of cutaneous interactive bases are given below.

BASE 1 Nutrient and moisturizing (gel)

PHASE A:

nutrient composition (amino acids, vitamins, trace elements)	qs 100
sodium salt of DNA	2-5%
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%

PHASE B:

mucopolysaccharides	20-30%
superoxide dismutase	0.5-1%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%

BASE 2 Refreshing and soothing (spray)

PHASE A:

nutrient composition (amino acids, vitamins, trace elements)	qs 100
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%

PHASE B:

citric acid	0.2-0.5%
trisodium citrate	0.5-2%

PHASE C:

rhamnose	0.01-5%

BASE 3 Radical-scavenging (cream 1) for greasy skin

PHASE A:	
tocopheryl acetate	0.2-2%
stearic acid	3-5%
squalene	2-7%
triglycerides	2-7%
PHASE B:	
water	qs 100
L-arginine	1-2%
glycerol	1-2%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%
PHASE C:	
nutrient composition (amino acids, vitamins, trace elements)	45-55%
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%
superoxide dismutase	0.5-1%

BASE 4 Moisturizing (cream 2) for dry skin

PHASE A:	
oleic acid	0.2-0.3%
palmitic acid	0.2-0.3%
behenic acid	0.2-0.3%
stearic acid	0.1-0.2%
linoleic acid	0.1-0.2%
arachidic acid	0.05-0.1%
triglycerides	0.1-0.2%
cholesterol	0.9-1%
cholesterol ester	0.02-0.04%
phospholipids	1.5-2.5%
squalene	3-7%

PHASE B:

water	qs 100
L-arginine	1-2%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%

PHASE C:

nutrient composition (amino acids, vitamins, trace elements)	45-55%
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%

PHASE D:

mucopolysaccharides	1-3%

BASE 5 Desensitizing make-up-removing (milk)

PHASE A:

stearic acid	2-5%
squalene	2-7%
triglycerides	2-7%

PHASE B:

water	qs 100
L-arginine	1-2%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%

PHASE C:

nutrient composition (amino acids, vitamins, trace elements)	45-55%
superoxide dismutase	0.5-1%
preserving system	0.9-1.1%
fucose	0.0005-1%

BASE 6 Moisturizing (lotion)

PHASE A:	
water	qs 100
L-serine	1-3%
glycerol	1-2%
urea	1-3%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%
PHASE B:	
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%

BASE 7 Dry (oil)

PHASE A:	
squalene	30-70%
triglycerides	30-70%

BASE 8, Bioprotective suncream

PHASE A:	
tocopheryl acetate	0.2-2%
stearic acid	3-5%
squalene	2-7%
triglycerides	2-7%
titanium oxides	1-20%
PHASE B:	
water	qs 100
L-arginine	1-2%
glycerol	1-2%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%

PHASE C:	
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%

BASE 9 Anti-sensitizing and regulating cleansing (milk)

PHASE A:	
stearic acid	2-5%
squalene	2-7%
triglycerides	2-7%
PHASE B:	
water	qs 100
L-arginine	1-2%
glycerol	1-2%
citric acid	0.2-0.5%
trisodium citrate	0.5-2%
PHASE C:	
preserving system (glucose/glucose oxidase/lactoperoxidase)	0.9-1.1%
phospholipids	2-10%
PHASE D:	
rhamnose	0.1-5%
fucose	0.0005-1%

The products according to the invention are, for example, in the form of a lotion, milk, cream, soap, etc., depending on their prescription or use. They are in a stable, single-phase, two-phase or three-phase topical form, for example.